**DEPARTMENT OF HOMELAND SECURITY**

**U.S. Customs and Border Protection**

**Notice of Issuance of Final Determination Concerning**

**Malarone Tablets**

**AGENCY:** U.S. Customs and Border Protection, Department of Homeland Security.

**ACTION:** Notice of final determination.

**SUMMARY:** This document provides notice that U.S. Customs and Border Protection ("CBP") has issued a final determination concerning the country of origin of Malarone tablets. Based upon the facts presented, CBP has concluded that the country of origin of the Malarone tablets is Canada for purposes of U.S. Government procurement.

**DATES:** This final determination was issued on July 2, 2018. A copy of the final determination is attached. Any party-at-interest may seek judicial review of this final determination within [INSERT 30 DAYS FROM DATE OF PUBLICATION IN THE FEDERAL REGISTER].

**FOR FURTHER INFORMATION CONTACT:** Ross M. Cunningham, Valuation and Special Programs Branch, Regulations and Rulings, Office of Trade, (202) 325-0034.

**SUPPLEMENTARY INFORMATION:** Notice is hereby given that on July 2, 2018, pursuant to subpart B of Part 177, U.S. Customs and Border Protection Regulations (19 CFR Part 177, subpart B), CBP issued one final determination concerning the country of origin of Malarone tablets, which may be offered to the U.S. Government under an undesignated government procurement contract. This final determination (HQ H290684) was issued under procedures set forth at 19 CFR Part 177, subpart B, which implements Title III of the Trade Agreements Act of 1979, as amended (19 U.S.C. 2511-18). In the final determination, CBP

concluded that the processing in Canada will result in a substantial transformation. Therefore, the country of origin for purposes of U.S. Government procurement of the Malarone tablets is Canada.

Section 177.29, CBP Regulations (19 CFR 177.29), provides that a notice of final determination shall be published in the **Federal Register** within 60 days of the date the final determination is issued. Section 177.30, CBP Regulations (19 CFR 177.30), provides that any party-at-interest, as defined in 19 CFR 177.22(d), may seek judicial review of a final determination within 30 days of publication of such determination in the **Federal Register**.

Dated: July 2, 2018.

Alice A. Kipel,
Executive Director,
Regulations and Rulings,
Office of Trade.

HQ H290684

July 2, 2018

OT:RR:CTF:VS H290684 RMC

CATEGORY: Origin

Nicolas Guzman
Drinker Biddle & Reath LLP
1500 K Street NW
Suite 1100
Washington, DC 20005-1209

Re: U.S. Government Procurement; Country of Origin of Malarone Tablets; Substantial Transformation

Dear Mr. Guzman:

This is in response to your letter, dated September 13, 2017, requesting a final determination on behalf of GlaxoSmithKline LLP ("GSK") pursuant to subpart B of Part 177 of the U.S. Customs and Border Protection ("CBP") Regulations (19 C.F.R. Part 177). A teleconference was held with counsel for GSK on June 8, 2018.

This final determination concerns the country of origin of Malarone tablets. As a U.S. importer, GSK is a party-at-interest within the meaning of 19 C.F.R. § 177.22(d)(1) and is entitled to request this final determination.

**FACTS:**

GSK is a global healthcare company that researches, develops, and manufactures pharmaceutical medicines, vaccines, and consumer healthcare products. At issue in this case are tablets sold under the brand name Malarone, which are indicated for the prevention and treatment of acute, uncomplicated *Plasmodium falciparum* malaria. GSK states that Malarone tablets have been shown to be effective in regions where other malaria drugs such as chloroquine, halofantrine, mefloquine, and amodiaquine may have unacceptable failure rates, presumably due to drug resistance.

According to the FDA prescribing information, Malarone is a fixed-dose combination of atovaquone and proguanil hydrochloride. *See* Prescribing Information, https://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b1_05_05_atovaquone.pdf (last visited Dec. 11, 2017). The chemical name of atovaquone 11 is trans-2-[4-(4 chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione and the molecular formula for atovaquone is C22H19ClO3. The chemical name of proguanil hydrochloride is 1-(4-chlorophenyl)-5-isopropyl-biguanide hydrochloride and the chemical formula for proguanil hydrochloride is C11H16ClN5•HCl. Each Malarone Tablet contains 250 milligrams of atovaquone and 100 milligrams of proguanil hydrochloride.

The FDA prescribing information also describes the microbiology or "mechanism of action" of atovaquone and proguanil hydrochloride. It states that atovaquone and proguanil hydrochloride "interfere with 2 different pathways involved in the biosynthesis of pyrimidines required for nucleic acid replication. Atovaquone is a selective inhibitor of parasite mitochondrial electron transport. Proguanil hydrochloride primarily exerts its effect by means of the metabolite cycloguanil, a dihydrofolate reductase inhibitor. Inhibition of dihydrofolate reductase in the malaria parasite disrupts deoxythymidylate synthesis."

GSK notes that atovaquone by itself is not indicated for the prevention or treatment of malaria. By itself, atovaquone is used for other purposes, such as the treatment of acute pneumocystis carinii pneumonia and cerebral toxoplasmosis. In contrast, proguanil hydrochloride can be used to treat malaria. However, GSK cites to several academic studies that conclude that the combination of atovaquone and proguanil hydrochloride provides a more effective treatment

compared to taking proguanil hydrochloride alone. GSK therefore states that atovaquone and proguanil are "synergistic in their mechanisms of action," resulting in the increased effectiveness of Malarone tablets compared to taking atovaquone or proguanil hydrochloride alone.

The manufacturing process for GSK's Malarone tablets begins in India, where the Malarone tablets' two active pharmaceutical ingredients ("APIs"), atovaquone and proguanil hydrochloride, are manufactured. After the two APIs are manufactured in India, they are imported into Canada for further processing at GSK's Mississauga, Ontario facility ("GSK Canada"). At GSK Canada, the two APIs are combined in a process that begins by producing a dry mix of the APIs, low-substituted hydroxpropyl cellulose NF, microcrystalline cellulose NF, and sodium starch glycolate NF. The dry mix is then combined with the following inactive ingredients, which are each sourced from the United States or a TAA-eligible country, to produce granules:

- Povidone K30 USP
- Polaxamer 188 NF
- Sofium Starch Glycolate NF
- Hydroxy Propyl Cellulose NF
- Purified Water USP
- Microcrystalline Cellulose NF
- Alcohol USP

Next, the granules are dried, milled into a dry powder, blended with magnesium stearate NF, and compressed into tablets. Finally, a film coat mix is added and the tablets are polished.

Once the manufacturing process is complete, the finished Malarone tablets are exported to a GSK facility in Zebulon, North Carolina. There, the tablets are packaged and labeled for sale to Prasco Laboratories, which markets and distributes the tablets under their own labeling as an authorized generic product under an agreement with GSK.

**ISSUE:**

What is the country of origin of the Malarone tablets for purposes of U.S. Government procurement?

**LAW AND ANALYSIS:**

CBP issues country of origin advisory rulings and final determinations as to whether an article is or would be a product of a designated country or instrumentality for the purposes of granting waivers of certain "Buy American" restrictions in U.S. law or practice for products offered for sale to the U.S. Government, pursuant to subpart B of Part 177, 19 C.F.R. § 177.21 *et seq.*, which implements Title III of the Trade Agreements Act of 1979, as amended (19 U.S.C. § 2511 *et seq.*).

Under the rule of origin set forth under 19 U.S.C. § 2518(4)(B):

> An article is a product of a country or instrumentality only if (i) it is wholly the growth, product, or manufacture of that country or instrumentality, or (ii) in the case of an article which consists in whole or in part of materials from another country or instrumentality, it has been substantially transformed into a new and different article of commerce with a name, character, or use distinct from that of the article or articles from which it was so transformed.

*See also* 19 C.F.R. § 177.22(a).

A substantial transformation occurs when an article emerges from a process with a new name, character, and use different from that possessed by the article prior to processing. A substantial transformation will not result from a minor manufacturing or combining process that leaves the identity of the article intact. *See United States v. Gibson-Thomsen Co.*, 27 C.C.P.A. 267 (1940); and *National Juice Products Ass'n v. United States*, 628 F. Supp. 978 (Ct. Int'l Trade 1986).

In determining whether a substantial transformation occurs in the manufacture of chemical products such as pharmaceuticals, CBP has consistently examined the complexity of the processing and whether the final article retains the essential identity and character of the raw material. To that end, CBP has generally held that the processing of pharmaceutical products from bulk form into measured doses does not result in a substantial transformation of the product. *See, e.g.*, Headquarters Ruling ("HQ") 561975, dated April 3, 2002; HQ 561544, dated May 1, 2000; HQ 735146, dated November 15, 1993; HQ H267177, dated November 5, 2016; HQ H233356, dated December 26, 2012; and, HQ 561975, dated April 3, 2002. However, where the processing from bulk form into measured doses involves the combination of two or more APIs, and the resulting combination offers additional medicinal benefits compared to taking each API alone, CBP has held that a substantial transformation occurred. *See, e.g.*, HQ 563207, dated June 1, 2005.

For example, in HQ 563207, CBP held that the combination of two APIs to form Actoplus Met, an alternative treatment for type 2 diabetes, constituted a substantial transformation. The first API, Pioglitazone HCI sourced from Japan or other countries, functioned as an insulin sensitizer that targets insulin resistance in the body. The second API, biguanide sourced from Japan, Spain, and other countries, functioned to decrease the amount of glucose produced by the liver and make muscle tissue more sensitive to insulin so glucose can be absorbed. In Japan, the two APIs were mixed together to form a fixed-combination drug called Actoplus Met. In holding that a substantial transformation occurred when the APIs were combined in Japan to produce Actoplus Met, CBP emphasized that "[w]hile we note that pioglitazone and metformin may be prescribed separately, the final product, Actoplus Met, increases the individual effectiveness of piofliazone and metformin in treating type 2 diabetes patients."

Similarly, in HQ H253443, dated March 13, 2015, CBP held that the combination of two APIs in China to produce Prepopik, "a dual-acting osmotic and stimulant laxative bowel preparation for a colonoscopy in adults," constituted a substantial transformation. Although the importer claimed that Country A-origin sodium picosulfate was the only API in Prepopik, CBP found that the Country B-origin magnesium oxide ingredient also qualified as an API. CBP further found that

taking Prepopik had "a more stimulative laxative effect" than taking each of the APIs individually and therefore held that a substantial transformation occurred when the APIs were combined in China.

Here, as in HQ 563207 and HQ H253443, two separate APIs are mixed to create a fixed combination drug that offers additional medicinal benefits compared to taking each API alone. The first API, atovaquone, is not indicated for the prevention or treatment of malaria. The second API, proguanil hydrochloride, is used to treat malaria, but is less effective than Malarone. This is because of the "synergies in [the APIs'] method of action," which result in a product that "interfere[s] with 2 different pathways" to prevent and treat malaria. Under these circumstances, the combination of atovaquone, proguanil hydrochloride, and inactive ingredients to form Malarone tablets in Canada results in a substantial transformation. The country of origin of the Malarone tablets is therefore Canada.

**HOLDING:**

The country of origin of the Malarone tablets for purposes of U.S. Government procurement is Canada.

Notice of this final determination will be given in the Federal Register, as required by 19 C.F.R. § 177.29. Any party-at-interest other than the party which requested this final determination may request, pursuant to 19 C.F.R. § 177.31, that CBP reexamine the matter anew and issue a new final determination. Pursuant to 19 C.F.R. § 177.30, any party-at-interest may, within 30 days of publication of the Federal Register Notice referenced above, seek judicial review of this final determination before the Court of International Trade.

Sincerely,

Alice A. Kipel, Executive Director
Regulations & Rulings
Office of Trade

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